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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07/10/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/768,479	Applicant(s) CORNISH, VIRGINIA W.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 May 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 91-96, 106-112, 119-133 and 141-154 is/are pending in the application.
- 4a) Of the above claim(s) 128-133, 153 and 154 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 91-94, 111, 112, 119-122, 125-127, 141-146, 151 and 152 is/are rejected.
- 7) ☒ Claim(s) 95, 96, 106-110, 123, 124 and 147-150 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input checked="" type="checkbox"/> Other: <i>JBC article (first page)</i> |

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (Paper No. 10, mailed on December 31, 2002), Applicants filed an amendment and response received on May 5, 2003 (Paper No. 11). Said amendment cancelled Claims 97-105 and 113-118, added new Claims 141-154, and amended Claims 91-93, 111, and 127. Thus, Claims 91-96, 106-112, 119-133, and 141-154 are pending in the instant Office action.

Election

2. Claims 91-96, 106-112, 119-133, and 141-154 are pending in the instant application. Claims 128-133 remain withdrawn from consideration as non-elected inventions. New Claims 153-154 are also withdrawn from consideration as being in non-elected Group III (see Paper No. 8 for complete restriction). Thus, Claims 91-96, 106-112, 119-127, and 141-152 will be examined herein.

Priority

3. As previously noted, the instant application is granted the benefit of priority for the continuation-in-part U.S. non-Provisional Application No. 09/490,320.

Drawings

4. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Art Unit: 1652

Withdrawn - Objections to the Specification

5. Previous objection to the specification for lacking updated continuity data in the first paragraph is withdrawn by virtue of Applicant's amendment in the form of a substitute specification with the appropriate amendments.
6. Previous objection to the specification and the Abstract for not completely describing the disclosed subject matter is withdrawn by virtue of Applicants' amendment to the specification.
7. Previous objection to the specification for having improperly cited references is withdrawn on the following points by virtue of Applicant's amendment in the form of a substitute specification with the appropriate amendments.
 - a) The Caldwell reference has been deleted; the objection is moot.
 - b) The DeGrado reference has been amended to no longer note "and following articles".
 - c) The Lin reference has been updated to include the citation instead of "in preparation".
 - d) The reference to "*The chemistry of b-lactams*", now Page, is now correctly cited.
 - e) The specification now contains proper reference citations.

Maintained - Objections to the Specification

8. Previous objection to the specification for having improperly cited references is maintained on the following points. Applicants' amendment to the specification in the form of a substitute specification is insufficient to obviate the instant objection, as argued by Applicants.

Correction is required.

- a) The references in the bibliography, beginning on page 63 of the substitute specification, are inconsistent in their citation with bold and italics used without clarity. Some references contain titles while others do not. The format of the bibliography must be consistent throughout.
- b) While clarification in the bibliography for multiple publications by the same author in the same year (Belshaw, Galleni, Stemmer, and Stockwell), has been amended, the

Art Unit: 1652

specification must also be amended to include citation to the proper reference. For example, on page 2 of the substitute specification, line 4, references to Stemmer 1994 do not indicate a or b as found in the bibliography. This is required for proper citation throughout the specification. See also Belshaw 1996 on page 3 and other examples throughout the specification.

- c) The Bolin reference in the bibliography on page 63 of the substitute specification remains incorrect. Filman is the first author and Hamlin is not an author as evidenced by the attached first page of the published journal article.
- d) Reference to the Lin reference on page 40 cites an incorrect publication year.

Appropriate correction for each point above is required.

Withdrawn - Objections to the Claims

9. Previous objection to Claim 91 for the misspelling "methorexate" is withdrawn by virtue of Applicant's amendment.

10. Previous objection to Claims 106-110 as depending from rejected claims is withdrawn in lieu of the new, independent objection below.

New or Maintained - Objections to the Claims

11. Previous objection to Claim 127 for having improper punctuation - the comma after "cerevisiae" - is maintained. In the amendment filed, a dash above a comma is present; this is also improper punctuation. No comma or dash is appropriate. Correction is required.

12. (new) Claim 95 is objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of Claim 93. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k). The only difference between the two claims is the side of "Y" that Dex

Art Unit: 1652

and Mtx are on; however, this is not described or claimed as a polar (i.e., 5' to 3') molecule.

Thus, a mirror image is equivalent. If this were not the case, Claim 95 and all its dependent claims could not properly depend from Claim 91 since the pattern of drawn structures throughout the specification has Dex on the left (H1 is Claim 91).

13. (new) Claims 106-110 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 106-110 require a complete structure of each dexamethasone and methotrexate. In each of the compounds claimed, at least a CH_2OH of Dex is missing and at least a $\text{COOH}/\text{CH}_2\text{CH}_2\text{COOH}$ of Mtx is missing. Thus, Claims 106-110 have Dex and Mtx analogs in the formula H1-Y-H2 and do not properly further limit the parent claim, Claim 95, that requires the complete structures of each dexamethasone and methotrexate. Appropriate correction is required. Claim 96 and new Claims 147-150 do properly limit from Claim 95.

14. (new) Claims 126, 141 and 142 are objected to for an improperly constructed Markush group. The claims read "selected from the group consisting of A, B, ... or F" when the proper Markush structure is ---selected from the group consisting of A, B, ... and F---. Correction is required.

15. (new) Claims 96, 123, 124, and 147-150 stand objected to for depending from objected or rejected claims.

Art Unit: 1652

Withdrawn - Claim Rejections - 35 U.S.C. § 112

16. Previous rejection of Claims 91-93, 97-105, and 111-127 under 35 U.S.C. § 112, second paragraph, is withdrawn. Applicants' arguments and the amendment have defined the term "analog" as purely a functionally similar compound without any particular structural relatedness to methotrexate. While such language is broad, it is not indefinite.

17. Previous rejection of Claims 92-105 and 111-127 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviations Dex, Mtx, LexA, and B42 is withdrawn. Applicants have amended the specification to define Dex and Mtx. Applicants argue that LexA and B42 are well known in the art as a DNA-binding protein and a specific activation domain, respectively. The Examiner agrees.

18. Previous rejection of Claims 119 and 121 under 35 U.S.C. § 112, second paragraph, as being indefinite for the parentheses around "DNA-binding domain" and "transcription activation domain" is withdrawn. Applicants argue that this format is common in the art; the Examiner agrees.

19. Previous rejection of Claims 97-105, 113-118 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's cancellation of said claims.

20. Previous rejection of Claims 91-94, 97-105, 111-122, and 125-127 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of the Examiner's reconsideration in view of Applicant's amendment.

Art Unit: 1652

21. Previous rejection of Claims 97-105 and 113-118 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicants' cancellation of said claims.

New or Maintained - Claim Rejections - 35 U.S.C. § 112

22. (new) Claims 91, 94, 141, and 143-146 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 91, the term "small" is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

23. Previous rejection of Claims 91-94, 111, 112, 119-122, and 125-127 under 35 U.S.C. § 112, first paragraph, written description, is maintained; moreover, newly added Claims 141-146 and 151-152 are added to the rejection to be: Claims 91-94, 111, 112, 119-122, 125-127, 141-146, and 151-152 are rejected under 35 U.S.C. § 112, first paragraph, written description.

Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that H1 moieties, claimed as an analog of Mtx that binds to DHFR, are adequately described because the art is replete with examples. The Examiner disagrees. Firstly, the term "analog" in the claims is only limited by its ability to bind DHFR since Applicants have made in clear in their arguments concerning the rejection under 35 U.S.C. § 112, second paragraph, for the word "analog" that a functional analog is intended, not a structural one. Thus, H1 is bounded only by function. As previously noted,

Art Unit: 1652

“To fully describe a genus of chemical compounds, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.” (emphasis added)

In the absence of structure as is the case here, physical and/or chemical characteristics OR structure/function characteristics are required to adequately describe product claims drawn to a genus of chemical compounds. In this case, merely functional characteristics are inadequate to describe the structure.

With respect to H2, Applicants argue that the term is bounded by a “portion of the compound to be tested for binding to a receptor”. Applicants note that because the H2 compound is *to be tested*, “the amended claims avoid any necessity that the specification provide any description of receptor-recognizing ligands”. The Examiner disagrees with this assessment. The instant claims are drawn to the compound itself, a chemical structure that must be defined by structure and function as defined in Lilly (see citation in previous Office action, Paper No. 10). Just because the claimed compounds are *intended* for use in yeast three-hybrid systems does not mean that the claimed compounds could not be used for other means, such as cancer treatments. It is precisely for these reasons that the compounds need to be adequately described by the specification. A facile means of the avoidance of this rejection for H2 would be an amendment of the pending claims to method claims.

With respect to “a binding domain capable of binding to methotrexate”, the arguments can be set forth against claims containing fusion proteins that have a binding domain to bind H1.

Art Unit: 1652

Applicants argue that the specification adequately describes the binding domain due to the examples in the specification and the "extensive knowledge in the art of domains that bind to methotrexate". Firstly, this binding domain can bind methotrexate and its analogs as long as the analogs bind DHFR; this genus is NOT limited to binding methotrexate specifically. Moreover, this again is purely a functional description for a claimed product. The issues brought up for H1 are reiterated here.

Applicants also argue that in light of *In Re Barr*, the functional language used in the instant case is acceptable. The Examiner disagrees with this interpretation of *Barr*. Specifically, the "capable" phrase Applicants refer to is an issue under 35 U.S.C. § 112, second paragraph in *Barr*. This instant case is one of written description, under the first paragraph. The Examiner has asserted that while the claim is broad, it is clear. The question remains of its adequate written description, which is not met due to the purely functional recitation in the claims to products.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

24. Previous rejection of Claims 92, 93 and 97-100 under 35 U.S.C. § 102(b) as being anticipated by Khawli *et al.* is withdrawn by virtue of Applicants' amendment and/or cancellation of said claims.

Maintained - Claim Rejections - 35 U.S.C. § 102

25. Previous rejection of Claims 91 and 94 under 35 U.S.C. § 102(b) as being anticipated by Khawli *et al.* is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicant's argue that an antibody is not a "small-molecule". Firstly, the

Art Unit: 1652

relative term "small" is rejected above under 35 U.S.C. § 112, second paragraph as being indefinite. Secondly, nothing in the claim requires the entire antibody to be considered H2. For example, a large portion of the antibody can be considered Y while the epitope, a small portion of the antibody, can be considered H2. For these reasons, the Applicants' arguments are not persuasive and the rejection is maintained.

Summary of Pending Issues

26. The following is a summary of the issues pending in the instant application:

- a) The specification stands objected to for having improperly cited references.
- b) Claim 127 stand objected to for having improper punctuation.
- c) Claim 95 stands objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of Claim 93.
- d) Claims 106-110 stand objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. This issue is raised by Applicants' amendment, which defines Dex and Mtx as exact compounds not including analogs thereof.
- e) Claims 126, 141 and 142 stand objected to for an improperly constructed Markush group.
- f) Claims 96, 123, 124, and 147-150 stand objected to for depending from objected or rejected claims.
- g) Claims 91, 94, 141, and 143-146 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "small".
- h) Claims 91-94, 111, 112, 119-122, 125-127, 141-146, and 151-152 stand rejected under 35 U.S.C. § 112, first paragraph, written description.

Art Unit: 1652

- i) Claims 91 and 94 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Khawli *et al.*

Allowable Subject Matter

27. The following is reiterated from the previous Office action for completeness:

“The instant application describes a yeast three-hybrid system with a specific example using a dexamethasone-methotrexate heterodimer. Yeast three-hybrid systems are useful in the discovery of previously unknown receptors for known ligands through efficient cDNA library screening. This system is described in USPN 5,928,868 (Liu *et al.*, IDS #4) using a dexamethasone-FK506 heterodimer, among others (see also Licitra *et al.* in IDS #4). While Licitra *et al.* teach the usefulness and broad applicability of their system, even specifically teaching the usefulness of high affinity ligand-receptor pairs (see page 12820), no indication of the usefulness of methotrexate as a ligand is found. Methotrexate is well known to have high affinity (picomolar range) for its receptor/protein, dihydrofolate reductase (DHFR). Pollock *et al.* (see PTO-892) is a useful review of the state of the art of yeast three-hybrid systems.”

Conclusion

28. Claims 91-94, 111, 112, 119-122, 125-127, 141-146, and 151-152 are rejected; Claims 95, 96, 106-110, 123, 124, 147-150 are objected to. Claims 128-133 and 153-154 are withdrawn from consideration as non-elected inventions. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

Art Unit: 1652


MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
July 8, 2003


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